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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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THE LATEST DEVELOPMENTS IN DRY CELL THERAPY (SICCACELL)

A. GRIFFEL, M.D.
Zurich, Switzerland.

INTRODUCTION

In July 1956, this journal printed an article by Doctor Hyman Goldstein entitled "Siccacell Therapy in Children". This was the first publication to appear in America on a new form of treatment which had already been extensively investigated, both experimentally and clinically, in several European countries. It was no mere chance that the first report on this therapy appeared in 'ARCHIVES OF PEDIATRICS'. The field of pediatrics is one in which it has achieved highly encouraging successes, particularly with those indications for which no effective treatment had hitherto existed: mongolism, encephalopathies and other developmental derangements.

When tentative trials were made towards the end of the 1940's in treating a small number of developmentally inhibited children with cellular preparations, a surprising fact was noted. The parenteral supply of foreign protein to these children produced practically no adverse reactions. What is more, it was observed after a few months that the appearance and behaviour of the children had undergone a marked change. The mongoloid aspect disappeared to an increasing extent, the intelligence quota increased

and a percentage of the young patients even became capable of schooling. It could now be hoped that some of these children would no longer be exclusively dependent on welfare institutions, but might become useful members of the community at least to a degree.

Encouraged by these initial successes, physicians proceeded to treat an ever larger number of children with cellular preparations, and more than 1000 cases are already on record today. Goldstein and Destunis have already reported their experiences in this journal and further publications by well-known pediatricians will probably appear in these pages in the near future. Therefore, the comments made below are intended to serve another purpose. They are designed to give the reader an idea of the essential principles underlying dry cell therapy. In view of the fact that there are few objective criteria for assessing its efficacy in the treatment of mongoloid and other developmentally deranged children, we wish to give the reader a survey of the investigations of cellular therapy in animal experiments and clinical studies in internal medicine. In this field, there are ample possibilities for applying objective test methods.

The aim of the following survey is, therefore, to indicate the potentialities and limits of this therapy, and give the unoriented reader a better idea of the prospects in treating developmentally deranged children. It may be that the reader will join us in reaching the conclusion that cellular therapy is at present the only possible form of treatment for devolopmentally retarded children.

In view of the large amount of material to be reported here, we shall refrain from giving a historical review of the development of organ therapy and shall deal directly with its most modern form, namely, dry cell therapy.

Every therapeutic agent, and particularly a biological treatment of this type, must fulfill two conditions: it must be harmless and it must be therapeutically effective. Since the manufacture of lyophilized cell preparations involves employing organs obtained from foetuses and young animals, there is the risk of transmitting zoonoses and other pathological organisms and the danger entailed in introducing foreign protein into the body parenterally.

The risk of transmitting disease can to a very large extent be met by strictly applying all known veterinary, serological and bacteriological tests on the animals before and immediately after slaughtering and also on the lyophilized preparations themselves, dried by freezing, before they are released for use. Tests are made to exclude all types of infectious organisms known to modern medicine.

Up to the present time, considerably more than 700,000 injections with dry cell preparations have been carried out, including several thousand in Switzerland, and as far as we know not a single case of infection attributable to the preparations has been observed. The number of cases with allergic manifestations to a slight or moderate degree is astonishingly small. According to experience to date, it amounts to less than 1 per cent of the cases treated.

A point of special interest is the reason why, after the introduction of foreign protein, allergic manifestations only occur in such a small number of cases. This fact alone is sufficient to merit the attention of medical research, quite apart from the question of therapeutic efficacy. It is suggested that foetal proteins and protein of young animals produce antigens, which can indeed provoke antibody formation in the human body, but that the reaction itself as a rule remains clinically subliminal.

Such antigen-antibody reaction has often been demonstrated by various workers (Kuhn and Knuechel, Grueber, Rother, etc.) whereby precipitating antibodies were demonstrated, which were specific for an organ, but not for the species. These findings agree with the investigations of other authors (Pressmann, et al.), who with the help of the isotope technique succeeded in demonstrating that certain antibodies were specific to a particular organ. For example, it was shown that kidney antibodies tagged with radioiodine were fixed nearly exclusively in the kidneys.

Whether, and to what extent, such an antigen-antibody reaction is related to the therapeutic effect has not yet been clarified. Also, there is still no clear proof as to the active principle as such. Present results in basic research in this matter suggest, however, that the active principle is bound to the cell and is not present in extracts, and furthermore that in the cell as a whole the mitochondrial fraction might be of special significance.

Thus, outside the realm of cellular therapy altogether, Lorenz

and coworkers in the United States have shown that total irradiation with lethal doses of x-rays is tolerated without difficulty by animals previously injected with bone marrow cells from an animal not irradiated. This protection fails if, instead of cells, only bone marrow extract is employed.

In order to clarify the question as to whether cell components, and if so, which components, enter into other cells, various experimental investigations were carried out (Lettré) with radioactively tagged cells.

It could be demonstrated that phosphate passes into the cell nucleus very quickly after administration of mitochondria, nuclear fragments and nucleic acids, whilst it is slower with inorganic phosphate and lipids. It is assumed that the nucleic acids of the cells also play an important rôle in cellular therapy. They are contained in the mitochondria as nucleo-proteins, and in view of their serological specificity might account for organ specificity. Attention is also drawn to the work of other authors (Dulaney, et al.) who demonstrated the serological specificity of nucleic acids of different origin.

Radioactively tagged cells were injected into pregnant and lactating animals and then the organs of the young animals were used for study purposes (Lettré). Specific activity could then be demonstrated in the corresponding organs of the young animals with a statistically significant difference from the radioactivity in the other organs. For example, following injection of brain cells, an increase in activity of 200 per cent was found in the brains of the young animals as compared to the other organs, and in the kidneys the increased activity due to tagged kidney cells lasted longer.

Gillissen and Hausmann have confirmed these results by trials with a complex of radio-cobalt and lung protein. The injection of ^{60}Co coupled to the homologous lung protein lead—with a statistically significant difference from the other animals—to a predominant enrichment in the lung of the test animal.

Lettré's studies on tumour cells are particularly interesting. When he injected the homogenate of tumour cells or fractions of it into animals with ascites tumour, there was a distinct increase in mitosis activity. Of the fractions, the mitochondrial fraction proved effective but the unstructured plasma did not. The nuclear fraction as a whole was also ineffective, but if the cell nuclei were

broken up, then these nuclear fragments also stimulated mitosis.

These results are similar to studies which Marshak carried out in the U.S.A. as far back as 1945. He worked with rats with regenerating liver and showed that the injection of chromatin from rat's liver accelerated growth and division of the cells. By using chromatin tagged with radioactive phosphate he was able to show further that this injected material was contained mainly in the chromosomes of the liver cells. This showed that injection of a cell component isolated by physical methods led to specific effects, to promotion of growth and absorption of material.

In this connection it should, however, be noted that so far all trials to achieve with cell fractions, as for instance with mitochondria, the same therapeutic effect as with the whole cell complex have failed. The effects of the whole cell are considerably more intensive and long-lasting than those with cell fragments.

Thanks to the great advances in biochemistry, histochemistry and electron optics, it is possible more and more to determine the direction of research, which has as its object a clear representation of the active principle. Although the results of basic research, to date, point to the special significance of the mitochondria or the nucleic acids contained in them, it must be supposed at the same time that the activity of these cell components is largely connected with various enzymatic processes within the cell, so that one is again inclined to consider the whole cell as the smallest basic unit of biological efficacy.

After consideration of the studies carried out with the aid of isotopes, some other noteworthy experiments may be mentioned.

Teir in Finland studied the effect of cell injections on the corresponding organs. The mitotic activity of the liver in older rats is practically non-existent. Teir injected such rats aged several months with liver cells from two-week-old rats. After only forty-eight hours he found a distinct increase in the number of mitoses in the organs of the recipients. But when he injected liver cells from twelve-month-old rats, no effect could be observed. In other words, only young liver proved effective. Teir obtained the same results after injection of skin, lacrimal glands and gastric mucosa. It was shown time and time again that the action was specific in that an effect was achieved only if cells of the corresponding organs were employed.

Harbers tested the therapeutic influence of cell preparations with

artificial damages on rats. By means of intraperitoneal injection of carbon tetrachloride (twice weekly during a period of 10-12 weeks) a damage of the parenchymatous tissue of the liver was provoked which is histologically similar to cirrhosis of the liver in humans. The group of test animals was injected with liver cell preparations and showed, in comparison to the uninjected animals, a significantly lengthened term of life. As indicator for the functionary state of the liver the bromsulphalein values were determined, which went down considerably with the test animals.

Grueber provoked artificial nephrosis in sixty rats by means of arsenobenzol. He injected 0.1 mgs. of neosalvarsan under the skin of the neck, five times in all. Half of the animals were treated with kidney cells a few days before and one day after the first neosalvarsan injection. With the treated animals the term of life was distinctly lengthened. The histological investigations showed very serious epithelium damages and necrosis in the glomeruli and tubuli with the untreated animals, whilst the pathological changes were only very slight with the test animals.

Maischein, Berlin, carried out serial tests on one hundred castrated male rats. In castration tests on rats the histological appearance of the pituitary provides a useful indicator for the changes which occur. In one group of animals he injected ovarian cells some months after castration, and at autopsy found the castration type of pituitary still present. Other animals received muscle cells, some were given heart cells, and in each case autopsy findings revealed the castration type of pituitary.

The last group, however, were given injections of testis cells, with the result that histological sections of the pituitary showed no changes characteristic of castration. Therefore, in castrated animals which receive injections of gonads of the same sex, the pituitary does not assume the character of a castration pituitary.

Neumann injected lyophilised ovary cells in a group of bilaterally ovariectomized mice and compared the results with the other group which had received pure follicle hormone (estradiol benzoate). The determinations were carried out with the aid of the Allan-Doisy test; thus the cell forms of the vaginal smear were investigated. With the hormonally treated animals the result was a rapid rise in the number of special cell forms (Schollenwerte) followed by a rapid drop in this number, within the space of a few days. In the animals which received ovarian cells there was a slow

rise in the number of special cell forms, but the effect lasted for six months.

Kment recently extended the same test procedure by injecting a third test group with placenta cells. The effect was still more impressive than after injection of ovarian cells in that the number of special cell forms was considerably higher for the same duration of effect.

It is difficult to explain how it is possible to produce such a lasting oestrus with ovariectomised animals. It is assumed that an effect occurs via the adrenal cortex or that there is a stimulation of residual tissue (Müller's path).

The experiments conducted by Maischein, Neumann, Kment and others are in themselves sufficient to show that the effective principle with *siccacell* therapy cannot be governed by hormone effects, since these are of only very short duration. Other authors, namely, Kuhn and Knuechel, have clarified this question, once and for all. These authors investigated in a large number of patients —there are now more than five hundred—the 17-ketosteroid elimination in the urine after injection of certain *siccacell* preparations. They used Dingemanse's method for determining ketosteroids by fractionating in a chromatographic column and obtained the following results: After injection of pituitary cells there was increased elimination of metabolites of all ketosteroid fractions. This is understandable, since the pituitary stimulates both the adrenal gland and also the gonads. After using suprarenal cortex cells, only the metabolites of the corticosteroid fractions were increased: dehydroisoandrosterone, aetiocholanolone, hydroxyandrosterone, and probably 11-hydroxyaetiocholandriol. After injecting testis cells, only the testosteroid derivatives were increased: androsterone and isoandrosterone. This selective increase in elimination attained its peak between the tenth and twentieth day, and even after months could be shown to be above the initial values. Such a prolonged effect cannot be the result of hormonal action, and in addition there was an increased elimination of hormone amounting to two hundred times the quantity of hormone in the cell preparations.

In order to obtain even more unmistakable proof that we are dealing here with a specific effect and not merely an unspecific stimulation by protein bodies, the authors injected other *siccacell* preparations also, for example heart cells, lung cells, muscle cells

etc., and were not able to observe any increased elimination of the 17-ketosteroids. It is true that after application of an unspecific stimulator, namely pyrifer, an increased ketosteroid elimination did occur when the adrenal gland was functioning normally, but this was very transient and after three days it could no longer be detected. Furthermore, using such an unspecific stimulator, it was only possible to provoke an elimination of the total ketosteroids, and not of the single fractions.

Within the scope of this paper it is not possible to report on all the work done to date in basic research, but the results already cited are extremely impressive. It can be stated with certainty that such effects cannot be explained on the basis of an unspecific stimulant or protein effect. Even though these above-mentioned results of experimental research work might not yet be taken as proof of the specificity of the effect, they nevertheless go far beyond what is generally observed with an unspecific effect. Basic investigations are at present being intensively pursued, and at university clinics and institutes in various European countries every effort is being made to shed more light on the as yet unsolved problems of the effect mechanism and the active principle involved. This basic research work has still another purpose to fulfil: it must offer proof that the amazing clinical successes achieved are not attributable to psychic mechanisms. During the last few years it has been proved—above all in America—that in 30-40 per cent of all cases treated with medicaments, the identical therapeutic results can be attained with placebo!

Psychic factors undoubtedly do play a part in therapy and with every healing process. The relationship of the patient to the doctor, the confidence that he has in his powers, the medical examination, the carrying-out of the treatment—any treatment—all these are factors which set favourable psychical influences in motion. And it is a good thing that this is so, because above all else we are doctors and the patient is not merely a retort for mixing various chemicals but a living personality. But it is essential for us to be quite clear in our minds as to what constitutes psychic effect and what is attributable to the medicament—in this case *siccacell* therapy. Clarity on this point is brought us by basic research and the "double blind test", where neither the patient nor the doctor investigating the results of previous therapy know what treatment has been applied. Such blind trials have been carried out on re-

peated occasions and have always resulted in decisive and objectively clear successes for *siccacell* therapy. Even the animal experiments were carried out partly by this method. In his tests on ovariectomised mice, Kment had the number of cells with a special form ('Schollenwerte') determined by two investigators who were given absolutely no information on the test procedure. Highly interesting checks were carried out on the work of Kuhn and Knuechel relating to the 17-ketosteroid determination after injection of *siccacell*. Heubner, former professor of pharmacology in Berlin, handed over to Kuhn and Knuechel a number of injection preparations, including placebo, which had been marked with special code numbers. Working solely on the basis of the 17-ketosteroid elimination, Kuhn and Knuechel then had to diagnose which preparations they had injected. At the last German Therapy Congress in Karlsruhe, Heubner confirmed that every one of the diagnoses was correct.

There are also certain other facts which go to prove that the effect of *siccacell* therapy is not due to psychic influences. This therapy was for example employed successfully in veterinary medicine. Dogs with eczema caused by endocrine gland trouble were cured; equally successful results were achieved in treating sterile cattle.

Reference must also be made to the successful treatment of children with encephalopathy, debility, mongolism and other developmental derangements. Here, the possibility of a psychic effect does not come into the question at all because such children are of course quite unaware of what is going on.

It is of especial interest to observe that after application of this therapy, the first result is a certain subjective aggravation, in consequence of the stress effect, which manifests itself during the first fourteen days. From the third week onwards there is a general revitalisation, whilst the specific therapeutic effect does not as a rule appear until after 5-8 weeks. The course followed by this effect is yet another factor which goes to prove that the curative process is not of a psychic nature. It is scarcely conceivable that psychotherapy would first lead to a subjective deterioration (fatigue, dullness, possibly depression) and that the successful result would not set in until several weeks had elapsed.

The specific stimulation of the diseased organ or system which occurs later can be clearly and objectively demonstrated in many

cases. The action is characterized by functional regeneration and demands, as a prerequisite, a sufficient quantity of healthy tissue capable of regeneration. Therefore, all cases should, a priori, be excluded from this form of treatment in which there is extensive anatomical destruction of an organ or which have been submitted to extirpation of an organ. It would be just as meaningless to test the effect of the dry cell preparation pituitary on a hypophysectomised patient as to try out stomach remedies on somebody after resection of the stomach. Treatment with dry cells is by no means to be considered as substitution therapy, and thus it differs basically from hormone therapy. The field of application is different for the two methods, and, therefore, they are to be applied only after an exact diagnosis.

Clinical experience accumulated up to the present has led to a narrowing down of the indications for this treatment, and in particular has shown that it is necessary to make a certain selection of the patients, based on exact diagnosis. Choosing the time for commencing treatment is also important. All acute inflammatory, hyperergic phenomena must have disappeared; the chronic degenerative phase must not have led, already, to irreversible alterations in the mesenchyma.

CLINICAL EXPERIENCE

Clinical experience can be summarized as follows:

The chief indication concerns circulatory disorders of an arteriosclerotic type, whether cerebral, coronary or peripheral in localisation.

The symptoms, due to circulatory disorders and angiospasm in the cerebral vessels, distinctly improve in many cases. Compared to therapy with vasodilatory drugs, the impression is that cell treatment exerts a more intensive and considerably longer-lasting action. It is contraindicated in cases of apoplexy, and should not be employed until three months after the acute attack. It may then be used as an additional method for relief of paresis and aphasia.

This form of therapy also appears to be superior in a certain number of cases to other medicaments in coronary sclerosis. Many cases are known in which patients were relieved of longstanding angina pectoris by means of dry cell therapy, where vasodilatory drugs had proved unsuccessful. Very severe cases of angina pec-

toris with threatening or not yet cicatrized infarct must be excluded, since the initial stress phase may lead to additional overburdening.

Peripheral vascular sclerosis behaves in the same way. Many cases show distinct improvement, with some astonishing results in the healing of incipient gangrene, but other cases do not respond to this therapy. Control by oscillometer only parallels the subjective improvement in a number of the cases. Patients are usually able to walk further, due to absence of intermittent claudication.

Taken as a whole, there are good results in about 60 per cent of circulatory disorders due to atherosclerosis. The effect of this therapy in Buerger's disease and Raynaud's disease cannot yet be assessed.

The most effective preparation in the treatment of circulatory disorders is placenta. Numerous investigations were carried out—especially on placenta extracts—in order to make a thorough study of the active substances contained in placenta. In addition to estrogenous and androgenous hormones, other steroid bodies also were found. Furthermore, certain extracts revealed the presence of an albumen fraction with amino-acids, which can be electrophoretically established; a very high alcalic and acid phosphatase content; a richness in mucopolysaccharides and others (Rauch, Zehnder, Koestlin). Nevertheless, the authors think that the factors which exert the greatest stimulating effect on the tissues still remain unknown. This stimulation seems to be an activation of breathing of mesenchymatous tissue. We think that the essential factor is bound to the cell itself, because the therapeutic effect of placenta cells is much more intensive and long-lasting than that of extracts. Clinically, placenta cells show a vasodilatory and antispasmodic effect and lead in a rather high percentage of the treated cases to a drop in the cholesterol, β-1-lipoprotein and β-globulin contained in the serum. These frequently observed clinical effects are confirmed and paralleled by the results of interesting animal tests. Hypercholesterolaemia was produced in sixteen rabbits, and eight of them were treated simultaneously with placenta dry cells. Repeated cholesterol estimations showed a distinct drop in the animals treated, and the autopsy and histological findings were particularly impressive. They showed in untreated animals the development of considerable atheromatous patches on the aorta

and coronary vessels, whereas in the treated animals these changes were, at best, just barely detectable (Dornbusch).

In many cases, when treating circulatory disorders, satisfactory results can be achieved with the preparation placenta alone. In various other cases, however,—especially when a circulatory disorder is due to Buerger's disease, and also in severe cases of atherosclerosis—the additional application of liver cells or even spleen cells is advisable. This is due to the reticuloendothelial structures contained in these preparations which appear to have an influence on the walls of the vessels by creating new capillaries.

Myocardial degeneration can often be beneficially treated by cellular therapy. The increased oxygenation which accompanies improved circulation appears to stimulate the metabolism of the heart muscle. Clinically, the effect manifests itself in a multitude of ways. Disorders of conduction are made to disappear in numerous cases, even in patients who had not formerly responded to medicamentous therapy. Patients refractory to digitalis or strophanthin often respond more readily to these when cellular therapy is given simultaneously or beforehand. *Siccacell,* therefore, acts, to a certain extent, as a basic therapy. This basic effect also reveals itself in the treatment of dysproteinemia. The protein in the serum is normalised, and due to the reascension of the albumen fraction, digitalis can again become effective.

Naturally, such favourable effects can only be observed in a portion of the cases, but these also include cases which do not respond to the classical medication. There are also certain patients on whom *siccacell* has no effect. Within the scope of this survey, however, we shall refrain from quoting statistics on successes and failures. Such figures are of little importance, and it is essential to bear in mind that *siccacell* is not intended to replace the traditional medicaments employed heretofore, but merely represents a supplementary therapy—an enrichment of the total therapy.

Nothing definite can be said as yet on the suitability of this method in patients with cardiac decompensation; distinct improvement has often been observed in cases of chronic decompensation, but cellular therapy is not to be recommended in acute cardiac insufficiency. Any acute cardiac inflammation is also a contraindication.

Myocardial degeneration is treated by intramuscular injection of lyophilised fetal heart cells (*Siccacell Heart*). In the majority

of cases, in addition, placenta cells are also used. In cases of dysproteinemia, liver cells might also have a good influence, whilst *hypothalamus* is quite effective given in addition to heart cells, where disorders of conduction are present.

It must be emphasized that *siccacell* therapy does not require prolonged treatment, nor a series of injections. As a rule, it is applied once only and, in exceptional cases, repeated after three, six or twelve months.

Among hepatic affections, chronic parenchymatous damages can be influenced. Chronic hepatitis responds quite well, the transition stage to cirrhosis also responds fairly favourably in many cases, but severe cirrhosis of the liver with decompensation does not. Cellular therapy is also contraindicated here by reason of possible haemorrhage from oesophageal varices. Acute hepatitis is also a contraindication. It cannot as yet be stated, with certainty, whether or not cellular therapy is superior to therapy with liver hydrolysates. Nevertheless, we know of several cases which could be improved after the usual treatments had failed.

In five cases of cirrhosis of the liver, an attempt was made by laparoscopy to discover whether dry cell therapy had produced genuine anatomical regeneration. In the first four cases, all severe forms of cirrhosis, the results were negative, whilst the fifth case, a transition form, showed evidence of regeneration. Treatment consists in intramuscular injection of fetal liver cells, often accompanied by additional injection of placenta cells and sometimes by application of stomach cells also. When there is a simultaneous insufficiency of adrenal cortex, cells of this organ also may be added.

The efficacy of this therapy in certain renal affections is noteworthy. Nephrotic syndrome responds best. Some cases which no longer reacted to ACTH showed a distinct improvement after cell therapy. In chronic nephritis with a nephrotic component, the chances of success depend on the nephrotic component being the dominant one. With regard to interstitial nephritis, nothing final can be stated as yet. As a rule, no success is to be expected in nephrosclerosis, and dry cell therapy is contraindicated in all acute renal conditions.

Nephrotic syndrome is treated by injection of fetal kidney cells (*Siccacell Kidney*) often accompanied by simultaneous injection

of placenta cells and sometimes, in cases of severe dropsy, even thyroid gland cells are added.

Siccacell therapy is of particular interest in the treatment of endocrine dysfunction, especially when there is insufficiency of the pituitary-diencephalic system.

The importance of the hypothalamus as a central switchboard for psychic, nervous and hormonal stimuli, and its regulating action on the hormonal secretions of the pituitary and the peripheral endocrine glands have now been investigated to a considerable extent. It would exceed the scope of this paper to refer to the numerous experimental and clinical studies with hypothalamus tissue and cultures; they have been reported in the extensive literature on the subject. We should, however, like to draw attention to one experiment which we consider particularly interesting. Rosenberg and Guillemin worked with pituitary cultures and they ascertained that a freshly removed piece of pituitary tissue continues to produce ACTH in the culture for 3-4 days. After this period, this secretion stops although the pituitary tissue keeps on developing and growing. If, however, after fourteen days a piece of hypothalamus tissue is introduced into the culture, without bringing it into direct contact with the pituitary, the pituitary tissue again starts producing ACTH.

But attempts to treat damage to the hypothalamus therapeutically have so far remained within modest limits. This is primarily due to the fact that with hormones it is possible to influence the peripheral endocrine glands, i.e., to substitute their function, without being able to repair the damage in the more centrally situated regulator in the hypothalamus. Even the pituitary must today be regarded functionally as a peripheral organ in relation to the hypothalamus. During the last war, it was often observed that following injury to the infundibulum or the hypothalamic nuclei by a splinter, untreatable cachexia developed even though the adenohypophysis remained completely intact.

The possibility of implanting hypothalamus tissue by means of dry cell therapy opens up interesting prospects for the treatment of those endocrine disorders which could not be dealt with satisfactorily until now. These include a number of cases of endogenous obesity—especially of the girdle and breeches type due to the hypothalamus—and also certain cases of dystrophia adiposogenitalis and Simmonds disease. As regards secondary amenorrhoea, we may even now look back on a large number of women

patients who have been successfully treated by this therapy. An exact diagnosis is of course absolutely essential: this type of treatment would not, for example, be employed for those cases of secondary amenorrhoea where it must be assumed that psychotherapy would be the only appropriate method. The chances of success with the treatment are also dependent on whether this insufficiency of the pituitary-diencephalic system is predominantly functional, and thus determined by a form of exhaustion, or attributable to extensive anatomical destruction. No great success could be anticipated, for instance, with Sheehan's syndrome when the pituitary is destroyed by widespread necrosis. An exact diagnosis is necessary both in order to determine whether this therapy is indicated and also to choose the appropriate preparation.

The main preparation employed in treating such symptoms of pituitary-diencephalic insufficiency is *siccacell hypothalamus*. But, according to each special case, other preparations, such as, for example, *gonads* or *pituitary*, might be added.

Myxedema and other symptoms of thyroid gland insufficiency can be improved by the injection of lyophilised thyroid gland cells provided there is still a sufficient amount of thyroid tissue to be stimulated. In a case of total aplasia of the thyroid gland, *siccacell* therapy is useless, and hormones or thyroid extracts are indicated.

Hypotonia, if due to diminished activity of the suprarenal cortex, can often be favourably influenced. In treating Addison's disease,this type of therapy cannot be very effective because of the anatomical destruction of the suprarenal cortex. So, it seems to be quite clear when hormones are indicated, and when, on the other hand, cells are indicated.

In gynaecology there are also interesting possibilities for the application of *siccacell* therapy. Secondary amenorrhoea, has already been mentioned above: as a secondary indication, we would also name insufficiency of the ovarian function accompanied by hypoplasia of the uterus.

In a great many cases, it is also possible to influence disturbances of the climacterium praecox and of the natural climacteric. Less satisfactory results, however, are obtained with the artificial climacteric. The treatment of such gynaecological indications is, in principle, carried out by using the preparations *placenta* and *ovary*, and sometimes, according to the case, with *hypothalamus*, whilst the injection of pituitary cells is not as a rule indicated during the premature climacteric and the climacteric proper because

in such women the pituitary gland is generally in a state of hyperfunction. *Siccacell* therapy is only indicated when there is a hypofunction of an endocrine gland.

There are also various investigations in progress to study the potentialities of this therapy in the treatment of male and female infertility, but it is still too early to express any definite opinion on this matter.

In pediatrics, lyophilised cell preparations are being used to an ever-increasing extent. Following initial trials of a tentative nature, large numbers of children with mongolism, encephalopathy and other developmental derangements are now being given this therapy. Today it may be safely stated that cellular therapy is the only possible treatment for such children. It is not necessary to emphasize that mongoloid children are not only a medical problem but also a social one and if one can enable them to do work of any kind, so that they are not entirely dependent on the assistance of charitable and welfare organisations, this alone is a gratifying result. This therapy aims—as first formulated by Haubold—at bringing underdeveloped organs to maturity. Thanks to the *siccacell* preparations, there is an unmistakable advance in the development of such children. Critics and doubters are not correct in asserting that certain signs of progress in these children represent a process of natural development. We are aware that the objective criteria for assessing a therapeutic effect with mongoloids and other developmentally deranged children are very limited. Nevertheless, various outstanding experts in this field have emphacised categorically that the improvements observed in the cases they have treated are unquestionably attributable to cellular therapy. We do not need to deal with the nature of these improvements in detail, since Goldstein and Destunis have already given a comprehensive report of their first experiences in ARCHIVES OF PEDIATRICS.

Their results are confirmed by authors in many other countries. In Germany, the foremost workers in this field are Haubold, Mommsen, von Schubert and others, who already have a dossier of several hundred cases. At the last Latin-American Congress on Neuropsychiatry which was held in Buenos Aires in October 1956, David gave a report on his first impressions concerning cellular therapy. The children treated by him included not only those suffering from mongolism and encephalopathy but also epileptics. It

was extremely impressive to hear that even epileptic children could be improved to a considerable extent through cellular therapy. Objective proof of these results was provided by means of electroencephalography.

Developmentally deranged children have also been successfully treated with lyophilised cell preparations in various other countries, but such cases are not sufficiently numerous to merit our dealing with them here. We ourselves—since our specialised field is internal medicine—have no experience of our own in this domain.

To sum up, therefore, at the present level of development of cellular therapy, this treatment can be employed with favourable chances of success for the following categories of indications:

Circulatory disorders due to atherosclerosis, and atherosclerosis in general;

Myocardial degeneration;

Chronic degenerative diseases of parenchymatous organs (kidney, liver);

Endocrine insufficiency;

Developmentally retarded children;

Premature senility.

Today, dry cell therapy is still in the initial stages of development. Basic research will have to be extended and intensified, and clinical trials on a large scale will be required before a final verdict can be given. But there is no doubt that dry cell therapy, because of its efficacy in certain indications, will take its rightful place among treatment methods.

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MYASTHENIA GRAVIS IN EARLY CHILDHOOD. (Arch. argent. pediat., 25:366-370, June 1954). Myasthenia gravis is rare in young children. The five cases reported by the author in children between the ages of 1½ and 4 years are the first reported in the literature of Latin American countries. The symptoms of the disease in children are the same as those observed in adults. In the early period of the disease the symptoms consist of extreme fatigue of the ocular muscles, with ptosis and ophthalmoplexia. The symptoms are mild in the morning and progress during the day to extreme paralysis in the evening. The diagnosis is confirmed by the positive results of the neostigmine (Prostigmin) test shown by disappearance of pseudoparalysis a few minutes after administration of an intramuscular injection of 1 cc. (one ampul) of a 1:2,000 neostigmine solution. In the subjects of this report the disease had appeared at a period that varied between 10 days and 6 months prior to consultation. In all cases the muscular symptoms were marked. They were unilateral in one case and bilateral in four cases. The treatment consisted of intramuscular injections of neostigmine, in daily dose of 5 mg., alone or in association with neostigmine given orally in daily doses of from one to three tablets of 0.01 gm. each, for a period of time that varied between three and four months. The treatment was discontinued in four patients who are considered cured. One patient is still under treatment, with progressive improvement. The author directs attention to the excellent results obtained in the reported cases. Myasthenia gravis seems to be due to a disorder of the neuromuscular synapsis from an unbalance of the cholesterinase-acetylcholine metabolism that is controlled by neostigmine. —*J.A.M.A.*

GROWTH PROBLEMS IN CHILDREN*

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When a child is brought to the physician because of poor growth, it is important to make a thorough study and ascertain whether he is really retarded in growth, and if he is, to determine the cause. Then, proper treatment can be determined. If there is no satisfactory treatment, the physician should so inform the parents and the child's record placed in a special file, so that the family can be notified if future discoveries provide a solution.

Three basic facts about growth must be kept in mind in considering growth problems. The potentials of growth are limited by heredity; the pace is regulated by the endocrine glands; and the environment determines how optimal that growth shall be.

During childhood, there are many normal variations in body build. Some of these are family or racial characteristics. The timing of puberty itself shows great normal variations. One boy may complete pubescence, whereas another shows no sign of even beginning puberty at the same age. Though the latter be short, he may yet develop a great growth spurt through puberty, eventually reaching average height or more. Nature has its own way of correcting growth discrepancies between the late and early maturer.[1] The early one tends to be tall at the onset of puberty and have a great growth spurt for only a short period. The late maturer, on the other hand, is usually small before puberty and has a slower growth rate over a longer period of time because the closure of the epiphyses of his long bones has been delayed. This permits growth for several years beyond the average range. These "late" children represent delayed activation of the pituitary, genital, adrenal systems rather than any specific glandular defect.

How can we tell if a child, who will be late in puberty, will have an increase in height at a later age? Observe two things: the growth of his testes and his bone age. If over a six month or one year period his testes increase in size, and his bone age is not much retarded, say only one or two years behind the average, then you can be pretty sure that the child will have a later spurt in

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growth at puberty. Even in a seventeen year old, if x-rays of the wrists and long bones show a bone development one or two years lower than his chronological age, you can reasssure him that he has one or two years of good growth ahead.

Another useful guide is the phosphorus content of the blood. As the bone growth reaches its end, the blood phosphorus approaches its adult level of 3.5 mgs. per 100 cc., and such a figure would indicate that very little further growth is to be expected. However, a blood phosphorus of 4.5 mgs. per 100 cc. or higher would signify there is much growth to come.

Because individual variations in growth within normal limits are so great, in judging any child's growth we must make use of comparative tables of height and weight at different age levels. The most useful charts give the percentile position of different heights at specific ages.[2, 3] Repeated records of the patient's height at intervals will inform us whether his rate of growth is within the normal channel for a child with his past record, or whether he is slowing down or advancing unusually in his growth. The Wetzel[4] grid chart is helpful in determining the patient's channel of growth. Other useful measurements are the span with the arms outstretched and the upper and lower measurements of the body as measured from the symphysis pubis;[5] bone age,[5a] as determined from x-rays of the hands and wrists is a very useful tool in studying children's growth. This guide is not absolute though, and a difference of one or even two years may often be disregarded.

Other important aids in diagnosing the cause of abnormal growth are afforded by laboratory tests. These help differentiate or pin point the various endocrine dysfunctions. For example, the protein-bound iodine of the blood and blood cholesterol give us a clue to thyroid function, often more useful than the basal metabolism rate, which is difficult to obtain in infants and children. X-rays of the skull may reveal the presence of a tumor, or pituitary abnormality. Glucose tolerance tests may confirm suspicion of pituitary deficiency, as will the adrenalin and ACTH eosinophile response. Determination of the 17-ketosteroids in the urine gives us knowledge of the adrenal secretion, and indirectly of pituitary stimulation of the adrenals. Where gonadal dysgenesis or eunuchoidism is suspected, the follicle-stimulating hormone (FSH) excretion in the urine may clarify the diagnosis.

Routine blood counts may reveal an anemia as a factor in poor growth, and routine urine may indicate a renal disorder or diabetes.

Of course, the physical examination may furnish the clue to the diagnosis. Sometimes the appearance alone suffices. For example, an achondroplastic dwarf is usually recognized by the short extremities and long body, the well developed shoulders and large head. The typical cretin likewise can be suspected by his appearance, as is the Mongolian idiot. The pituitary giant and the panpituitary dwarf are also easily spotted.

As retarded growth is a sign of disordered physiology, the etiological diagnosis begins with the taking of a thorough history. The family background is important in helping us determine how much of a role heredity plays. Naturally, if both parents are tall, very short stature in the child is of more concern than if both parents are short. Details of the parents' stature at the child's age is useful. If the parents were late maturers whose great growth spurt occurred after puberty, they can be reassured that their offspring may have a similar growth pattern. If the patient's growth proceeded normally for several years, and then slowed its pace, we must rule out chronic infection, poor nutrition, anemia, renal or digestive disease, and endocrine dysfunction, particularly of the thyroid and pituitary gland.

ETIOLOGICAL CLASSIFICATION OF INADEQUATE GROWTH[6]

1. Genetic or constitutional factors:
   a. Primordial dwarf
   b. Normal small stature.
2. Delayed adolescence with a retarded growth spurt.
3. Bone diseases:
   a. Achondroplasia
   b. Rickets or renal rickets
   c. Osteogenesis imperfecta
   d. Diseases of the spine.
4. Nutritional:
   a. Hypocaloric
   b. Vitamin deficiency
   c. Inadequate utilization of food, as in coeliac disease, diabetes, liver or kidney disturbances and anemias.

5. Infections:

   Tuberculosis, intestinal parasites. Any severe disease, diseased tonsils, chronic infection.

6. Circulatory:

   Disturbances and anomalies of renal system. Congenital cardiac, fibrocystic pulmonary disease, polcystic kidneys, Fanconi's syndrome, pulmonary or cardiac conditions.

7. Endocrine diseases:
   a. Hypothyroidism
   b. Hypopituitarism
   c. Diabetes
   d. Mixed Types
   e. Excess hormones producing precocious epiphyseal closure.
      1. Puberty precox—testes tumor—ovary tumor, ovarian agenesis. Adrenogenital syndrome, Cushing's syndrome—Albright's disease, precocious puberty with osseous fibrodysplasia.

8. Unclassified:
   a. Progeria
   b. Severe brain defects
   c. Mongolism.

The primordial dwarf is usually born small and grows slowly. His stunted growth is not due to any endocrine disturbance, but is an inherited trait, although it may occur in normal families as well as those with dwarfed members. Epiphyseal development is normal, mental average, good; sexual development occurs at the usual time, and their features mature during adolescence, unlike the pituitary dwarf whose face remains childlike after adolescence. Thus, the primordial dwarf develops into a miniature adult, normal in all respects except size. There is an entire race of pigmies in Australia who are primordial dwarfs.[7] There is another race of very short people, the Vicos Indians living in the Andes of Peru whose short stature is not inherited but is due to the poverty of their soil, their diet and sanitary facilities.

The pituitary dwarf frequently appears normal at birth and continues to grow at an average pace the first few years of life. Then he becomes stunted and growth slows down considerably.

In the pituitary dwarf, the upper measurement from the symphysis pubis becomes equal to the lower at an early age, even three or four. Normal body measurements do not assume this proportion until ten or eleven. His bone age is also retarded, and the epiphyses of the long bones may remain open as late as 22 to 25 years. The face remains doll-like, the voice retains its high pitched thin quality, and the genital and sexual development is poor.

The pituitary gland, although it may be influenced by the hypothalamus, is the leader of the growth glands, and its hormones stimulate the thyroid, testes or ovary and the adrenals. Thus the pituitary dwarf has diminished secretion from all these glands. The blood protein-bound iodine is slightly low, as is the FSH and the 17-ketosteroid output of the urine. A useful test in differentiating pituitary failure from hypocaloric or functional dwarfism is the adrenalin eosinophile response, which is poor in hypopituitarism. Also, the insulin tolerance curve is flat in hypopituitarism. X-rays of the skull, although frequently normal, may reveal a very small sella turcica, or the encroachment of a tumor on the pituitary gland or the hypothalamus.

There are many grades of dyspituitarism, and in spite of all laboratory tests, you occasionally cannot make a definite diagnosis. In these doubtful cases, it is best to keep the patient under observation without endocrine therapy for one year. If, in spite of a high caloric diet, with high protein mineral and vitamin content, especially B-12, his growth is not improved, he may be treated for a pituitary deficiency.

Unfortunately, until now, there has been no anterior pituitary growth hormone effective in humans. Ephraim Shorr[8] and his associates at the New York Hospital did report two children who developed a positive nitrogen balance when given large amounts of anterior pituitary growth hormone, but there was practically no increase in height. There is new hope of an effective growth hormone.

Only a few months ago, Dr. C. Li[9], at the Hormone Research Laboratory of the University of California, succeeded for the first time in increasing the growth rate of monkeys, rats, and humans by using an extract of human and monkey pituitary glands. At present, this is available only for experimental purposes, and in extremely limited quantity.

Almost always, the hypopituitary child also has a mild hypothy-

roidism so that thyroid gland extract is used in the treatment, but it is not effective in promoting growth in these children. Genital development is usually poor, and testosterone does help this condition. Testosterone also has the effect of diverting protein from catabolic to anabolic channels and produces positive sodium potassium, phosphorus and other chemical balances.

However, testosterone also causes early closure of the epiphyses, so the ultimate height reached may not be greater than if untreated. One way of getting around this is to alternate three months of treatment with three months without any androgens. It is questionable whether this succeeds. Metandren linguets may be used, 10 mgs. to 20 mgs. daily. Some prefer the gonadotropic hormone obtained from pregnant mare's urine, Equinex (Ayerst). One thousand units are given three times weekly for three weeks, then twice weekly for two weeks. This results in an increase in the size of the penis, testes and pubic hair, but it also hastens epiphyseal closure. Unless psychological factors demand the early use of androgens, therefore, it is best to postpone their use until adolescence or thirteen years of age. There is another preparation, Nilevar (Searle), which is said to produce its anabolic effect with only slight androgen production. The first ten days 1 mg. to 1/5 mg. per kilo are given daily, then 0.5 mgs. per kilo daily in three to five doses. We are awaiting results of further experiments.

In the female pituitary dwarf, little can be done to increase the height. The pituitary stimulus to the ovaries is deficient and estrogen and FSH are low in such a girl. Untreated, she does not develop breasts, public hair nor menstruate. Estrogen administration develops breasts and causes enough adrenal stimulation for pubic hair. By cyclic treatment with estrogen,[10] periodic bleeding may be produced to simulate menstruation. The first three weeks, 1 mg. stilbesterol are given daily, and bleeding should occur two to five days after withdrawal of estrogen therapy. This is of enormous psychological advantage. These girls may marry later and have sex relations, but, nearly always, they are infertile. X-rays of the skull, although usually normal, may reveal a craniopharyngioma pressing on the pituitary or hypothalamus. Surgery is rarely successful, but occasionally it is advisable. Usually, no treatment is indicated for the tumor, unless there are pressure symptoms or impaired visual fields.

The most common cause for growth retardation is insufficient nutrition. Dr. Nathan Talbot[11] and his associates at the Boston Children's Hospital Endocrine Clinic studied one hundred consecutive cases brought for growth retardation, and found poor nutrition responsible for fifty per cent. Just how this influences growth is not entirely understood, but evidence in rats indicates that the pituitary and thyroid gland decrease in size during starvation, especially when on low protein diets. It is possible that there is a disturbance of the appetite or satiety centre[12] situated in the hypothalamus.

If malnutrition is corrected early enough, growth may proceed at a rapid pace and make up for the poor former rate of growth. But if the poor diet has existed for a long time, the child's growth may not respond to dietary treatment. This was evident in the study of refugee children at Stuttgart, Germany.[13a] They presented a picture of retarded growth similar to hypopituitarism. Some recovered slowly. But in others the damage (to the pituitary) was irreparable. If left alone, most of these malnourished children will stop growing before they reach average adult height. However, some may progress slowly on their own and even develop a late spurt in adolescence often to become taller than the average.

Older children with hypocaloric dwarfism are frequently tired, become irritable, are often anemic, have a dry skin and develop poor musculature and posture. After the diagnosis has been made by exclusion, the final test is to produce a rapid gain in weight and height within six to twelve months by the treatment. Norman Wetzel[13] has shown that insufficient diets may be found among well-to-do children as well as poor ones. Adding 25 mgs. vitamin B-12 daily to their diet caused an increase in height, averaging three inches or more a year, a half inch more than the average, equivalent to an extra six months growth.

Besides a high vitamin diet, B-12[14] in particular, high calory diets are used, 2500 to 3000 per day, for children over six, with particular emphasis on proteins and minerals. Thus meat, fish, eggs, and cheese are emphasized. Protenum may be used to increase protein intake. Each serving provides 25 grams of protein. Iron is added if anemia is present, and calcium if less than 24 ounces milk daily is consumed. To supplement the calory intake, a concentrated high calory product like Lipomul (peanut

oil emulsion) or Morcal (coconut concentrate) may be given. Extra milk is given between meals and at bedtime.

Emotional factors[15] responsible for poor appetite must be corrected, and living conditions made as optimal as possible, with sufficient sleep, exercise, fresh air and sunlight. If weather permits little sunshine, a sun lamp may be used. Any diseases found should be treated, bad tonsils removed. If digestion is impaired because of coeliac disease, this must be treated. Allergic children often suffer from insufficient calories and protein because of their restricted diet.

Liver,[16] which like vitamin B-12 is useful in improving the growth rate of rats, has been tried for children but without significant success. Similarly, antibiotics, like aureomycin have succeeded in promoting growth in chicks, but not in humans. It is thought that by destroying intestinal bacteria which produce substances interfering with growth or which use up enzymes needed for growth, height increases at a more rapid rate. However, reports of aureomycin in children have not been encouraging. Ataraxic drugs may help the emotionally disturbed child.

Next to insufficient nutrition, the most common cause of growth retardation seen in endocrine clinics is hypothyroidism. The classical cretin will rarely be missed, with his typical facies, thick protruding tongue, dry skin and hair, umbilical hernia and tendency to constipation, delayed dentition and mental retardation. However, there are lesser degrees of hypothyroidism in infancy which are not easily diagnosed. Even in the cretin, hypothyroid symptoms rarely show up before the second or third month, for the maternal thyroid secretion may carry the newborn over this period. Then his inability to produce his own thyroid hormone secretion produces signs of hypothyroidism, that is, dry skin, thick tongue, hypotonicity, constipation, and slow development make one suspicious. Fortunately today we do not have to rely solely on our clinical judgment. The protein-bound iodine of the blood and blood cholesterol help confirm the diagnosis. X-rays of the wrists show retarded bone development, whereas in the hypocaloric dwarf, bone age is usually greater than height age. Response to thyroid therapy is the final proof. If the length increases more than six centimeters in two months of thyroid treatment, the retardation is due to hypothyroidism. If the blood cholesterol is high, and drops 40 per cent or more after thyroid treatment, hypothyroidism

is confirmed. Early diagnosis and treatment is important because unless exogenous thyroid is given after the first few months of life, irreversible damage to the nervous system and consequent mental retardation may be inevitable. Average or even better mental development is possible if treatment is started by two or three months of age.

The older child with hypothyroidism is likely to be thin, not fat. He complains of fatigue, cold clammy hands, dry skin and hair and perhaps constipation. The body temperature is apt to be low. To confirm this, the temperature should be recorded three times daily for one week. X-rays of the wrists shows markedly retarded bone age and sometimes stippling and fragmentation of the epiphyses. The body retains its infantile proportion, the length from symphysis to head being greater than to the floor. The pituitary dwarf has adult proportions of equal length from the pubis to head and foot early in life, at a few years of age. The PBI. and blood cholesterol help confirm the diagnosis. Basal metabolism is difficult to obtain in young children, and generally less helpful than the PBI. Increase in the PBI. is a valuable guide in appraising therapy. Usually we start with a quarter grain thyroid gland increasing every two weeks until the maximum effect has been obtained without toxicity.

Even a totally athyroid child can usually be made euthyroid with a dose of 90 mgs. to 100 mgs. thyroid per sq. meter or maximum of three grains daily. If diagnosis is made early enough, and treatment persisted in constantly without lapses, ultimate growth may be normal and even mental development good, although this cannot be counted upon.

Paradoxical as it may seem, sexual precocity is a cause of growth retardation. Both in the male and female, such patients have early closure of the epiphyses of the long bones which limits their further growth. Although they are tall for their present age, they end up as short individuals. The most common form of sex precocity is the constitutional, in which the sex gland development occurs early, but without any pathology in the adrenal or sex glands. In the male, the testes as well as the penis is enlarged, public hair develops early, acne and an adult voice may be present even at seven years or less. The bone age is advanced and musculature enlarged. In the female with precocious puberty and early menses, the epiphyses also close early and they become short adults.

We are unable to prevent this in the female, but in the male, we can delay the closure of the epiphyses and thus permit further height by injecting a choriogonadotrophic hormone of another species than human, like the hog's.[17] This acts as an antagonist to the FSH or gonadal hormone and inhibits closure of the epiphyses, but does not interfere with the growth hormone. It may take two or three months of intramuscular injections of 25 units three times weekly for the antihormone to develop. The injections are continued until the maximum effect has been obtained. The patient's serum is then tested for antihormone level by adding the serum to FSH in a rat. The rat's ovary remains the same size if antihormone has been developed. If not, it doubles or triples in size and weight.

The 17-ketosteroids are normal or only slightly increased in constitutional sex precocity, but in adrenal hyperplasia or tumor, it is markedly increased. Such children have penile enlargement and early pubic hair, but the testes are not similarly increased in size, and spermatogenesis nearly always does not occur. Females with tumors of the adrenal are born normal and later develop virilization with clitoral enlargement and sex hair development. Cortisone suppresses the high 17-ketosteroid excretion in adrenal hyperplasia, but not in adrenal tumors. Ovarian tumors which give rise to precocious sex development may usually be palpated, and the estrogen excretion is excessive, with normal 17-ketosteroids. Testicular tumors also can be felt. Pineal and hypothalamic lesions sometimes cause sex precocity. Surgery offers the most hopeful approach to tumor cases, and if successful, growth develops at a normal pace.

Gonadal ovarian agenesis is a rare cause of short stature in girls, and usually is recognizable. The appearance is characteristic —the face is adult-like, the forearms are held at a wide angle to the arms, they often have a webbed neck appearance, and abnormalities are common such as coarctation of the aorta. The breasts remain infantile, as does the uterus if untreated, and there is no menstruation. The bone age is retarded less than their height age. Urinary FSH is very high, ketosteroid excretion normal or decreased. By estrogen treatment these girls develop breasts and can be made to menstruate, but they remain short individuals, usually 56 inches or 57 inches tall. Of course, they cannot have children.

There are three types of unusually tall children—the constitutionally tall stature, by far the most common; the hypogonadic or eunuchoid, and pituitary gigantism.

The normally tall child of tall parents, whose proportions are normal, needs no correction for his height, but only good emotional and psychic adjustment to it.

Parents of a tall girl sometimes ask what can be done to prevent further growth. Usually it is enough to reassure the parents and girl that she has reached 96 per cent of her final adult height once she has had her first menses. For the rare instances where help is indicated, x-ray radiation to the pituitary gland has been tried. Generally, this procedure is condemned as it also may result in pituitary products being diminished other than the growth hormone. Some endocrinologists have induced menstruation by cyclic use of estrogens in order to cause earlier closure of the epiphyses of the long bones, and so stop growth. Such girls should be observed very closely, and it is best to reserve such experimentation for the experienced endocrinologist. It is helpful to do a fasting phosphorus content of the blood in these patients, and if near 3.5 mgs. per 100 cc. the adult level, you can be sure that growth will not proceed much further. If high, further growth may be expected, and inducing menstruation may be worth consideration.

When genital retardation is accompanied by great increase in height, with long extremities, one suspects a eunuchoid cause. The body span is usually larger than the height in such children. In boys, if the FSH is high, one is probably dealing with testicular failure and a testicular biopsy may clarify the situation. The breasts may become enlarged also, as in Kleinfelder's syndrome with failure of spermatogenesis, poor testicular development and decreased 17-ketosteroids.

In pituitary gigantism, x-ray of the skull may reveal evidence of a tumor in the pituitary region. Visual fields may not be affected nor cerebral pressure symptoms occur until the tumor has grown much larger. The serum phosphorus is high, and a level of 6.5 mgs. per 100 cc. after 12 years of age should make one suspicious. The epiphyseal lines remain wide open until 25 years or even 30 years of age. The condition is extremely rare in childhood, and is usually not observed until after puberty. However, rarely, one comes across a young child who grows at a normal pace, and then suddenly shoots up to great height. One such girl, an identical

twin of eleven years, grew eight inches within four months, while her twin sister increased only a half inch. X-rays revealed a huge sella turcica and changes in long bones characteristic of pituitary increase. Cautious x-ray radiation may stop such excessive rate of growth. If visual fields or cerebral pressure symptoms occur, surgery may be considered. It is sometimes successful and growth proceeds at a normal pace after the tumor is removed.

There are other rare growth problems such as Cushing's and Fanconi's syndrome, Laurence-Moon Biedl syndrome, progeria, and Albright's disease which are beyond the scope of this paper, and so will not be discussed.

One sees puzzling variations in growth disturbances; not all cases are clear cut and typical, but in nearly all a careful study as outlined in this article will indicate the cause of the disturbance or abnormality and suggest the proper treatment. With the development of the pituitary growth hormone from monkeys and human glands, hope of success is greater for many of the retarded growth patients. For the patient who cannot be helped, the physician must improve the psychological acceptance of his size and encourage the patient to develop his personality and abilities so that he can still get the most out of life.

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Obituary.

It is with the deepest regret that the Editor and the Editorial Board of the ARCHIVES OF PEDIATRICS announce to its readers the death of Edwin Cuyler Treat, President of E. B. Treat & Co., Inc. and publishers of the ARCHIVES OF PEDIATRICS for over fifty years.

EDWIN CUYLER TREAT.

In the death of Mr. Treat, the ARCHIVES OF PEDIATRICS has lost a friend and an associate who will be sorely missed.

Born in New York City 84 years ago, he attended City College of New York and was graduated from Wesleyan University in 1894. Public spirited, he had diversified interests and was a member of various fraternal organizations and clubs.

Published by his father in 1884 under the family name of E. B. Treat & Co. Inc., the ARCHIVES OF PEDIATRICS was the first medical journal in English to be solely devoted to the field of pediatrics, and for many years it was the only medium for the written diffusion of knowledge concerning this specialty. Among the contributors and collaborators were such famous names as Sir William Osler, Drs. L. Emmett Holt, Linnaeus Edford La Fétra, John Howland, Joseph Brennemann, etc.

In his lifetime, Mr. Treat fostered a high standard, and it will be the aim of the ARCHIVES to maintain the same high quality and the medical integrity of the publication.

PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

HEMORRHAGE OF SYPHILITIC ORIGIN IN THE NEWBORN*

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The existence in the newborn of a tendency to leakage from the blood-vessels in the presence of abnormal conditions is a matter of common observation. The blood at this period is the most unstable of all the tissues, probably from the fact that it is undergoing the transition that marks its change from fetal to mature blood. The extravasations which are common in the neonatal period depend upon developmental conditions, as hemorrhages of this character are not manifest at birth, except as the result of trauma, and cease to be observed after the first few weeks of life. This is corroborated by the fact that prematurity and conditions of subdevelopment predispose to such hemorrhages.

Without disregarding other causes it has been demonstrated that certain hemorrhagic conditions are the accompaniment in the newborn of the more commonly recognized evidences of syphilis. A direct infection transmitted in antenatal life has been proven by the history in individual cases. Although syphilis in the fetus may so affect nutrition as to interfere with development, the form of syphilis in the newborn in which hemorrhage occurs is not necessarily accompanied by cachexia, as the infants may be well nourished. It bespeaks, therefore, a constitutional tendency.

* Read before the Philadelphia Pediatrics Society, December 13, 1904.

** At the time of writing this paper, the author was Visiting Physician to the Philadelphia Lying-in Charity, Philadelphia, Pa.

Reprinted from Archives of Pediatrics, 22:43-51, January 1905.

As to the terminology, there seems to be a tendency to accept the term purpura as applicable to hemorrhagic conditions in the newborn. This designation, however, should include not only the skin hemorrhages, but internal extravasations. On the other hand, it would hardly be proper to apply to the general hemorrhagic conditions observed in the newborn the term purpura hemorrhagica which is reserved for the severe conditions seen at a later period. It appears, therefore, that the latter term should remain as a special designation, notwithstanding its applicability to the majority of instances of bleeding in the newborn.

The term syphilitic purpura is applicable to those purpuric conditions which are due to syphilis, but in accepting it, the tendency in syphilis, as in other conditions marked by hemorrhage in the newborn, to general bleeding, in contradistinction to skin hemorrhage, should be borne in mind.

The term hemophilia is inapplicable to the hemorrhagic conditions which enter into the differential diagnosis of syphilis in the newborn. Hemophilia is a later manifestation and bears evidences of being an hereditary tendency. It usually affects male children. This is not gainsaying the fact that persistent wound hemorrhage may occur as a complication of purpura (*vide,* A Case of Icterus Neonatorum with Purpura and Persistent Hemorrhage from a Punctured Wound, J. E. Talley, ARCHIVES OF PEDIATRICS, (p. 695), September 1904. The writer has observed one instance of oozing from the skin in a syphilitic infant. The lower lids and the flexor surfaces of the ankles were the points from which oozing took place.

The term "Hemorrhagic Disease of the Newborn," which has been adopted by Townsend and Rotch, implies a condition dependent upon a special pathological change, such as is seen in acute fatty degeneration of the newborn; whereas, the hemorrhagic tendency in the newborn is due to a variety of causes and is incidental to the development of this age. For this reason we may speak of it as a diathesis rather than a disease.

Syphilis in itself, where it can be proven to exist, is in all probability not the primary cause of hemorrhage. It is more probable that the constitutional effects of syphilis underly the degenerative changes in the blood and vessels, which lead to hemorrhage. The maternal evidences of infection are often obscure; the infection may be transmitted directly from the father and present no evi-

dences in the mother, or the history may be misleading on account of the ignorance of the parents. In a case reported by L. E. Frankenstall, it appeared reasonable to connect the hemorrhagic condition in the infant with the existence of tabes in the father, an antecedent condition which would have been entirely overlooked if the history had not been carefully investigated.

As to frequency, among 3,364 children born at the Philadelphia Lying-in Charity, between the years 1901 and 1904, there were forty-five instances of hemorrhage, the majority of which were fatal. Among this number of infants there were ten in whom the history of syphilis was either obtainable in the parents, or the clinical or postmortem evidence of syphilis was present in the children themselves.

Leakage may occur from the minute blood vessels in the skin, mucous surfaces, the serous membrane, the meninges and brain, and the parenchyma of the various organs and glands. Hemorrhage may appear also from the conjunctiva, the ears and umbilical cord. The skin hemorrhages may be in the form of oozing from the capillaries, very often seen occurring from the roll of skin which surrounds the cord. Bleeding may occur also from fissures at the mouth or anus. It may take place in the vesicles in pemphigus or from the base of the vesicles after rupture. Extensive extravasations between the skin usually affect dependent portions of the body, as the feet and ankles, also those surfaces which are exposed to pressure after birth, as the dorsal region, the buttocks and the extensor surfaces of the arms.

Extensive hemorrhage in the lower region of the abdominal wall and the scrotum or vulva is consequent to the ligation of the cord. A review of the fetal circulation will recall the fact that interference in the current of the umbilical arteries will reduce a backward pressure in the iliac arteries, which affects their distributing branches, resulting in extravasation in the regions supplied by the latter. This brings us to the question whether there may not exist a general heightened arterial pressure in utero as a result of obstruction in the placental circulation due to obliterative changes in the vessels. Not only are the placental vessels affected by the syphilitic changes but those of the cord as well. It is even conceivable that torsion of the cord, frequently observed in instances of intrauterine syphilis, may have the effect of increasing the resistance in the fetal circulation. As a consequence of these

various factors we may conceive of a condition of heightened pressure which shows its result at the time of birth when the demands upon the circulation are suddenly increased.

The extent of the hemorrhage varies. In the skin the epidermal layer may be invaded by extravasation in the form of petechiæ. A more extensive hemorrhage is apt to occur in the corium, elevating the epidermis. The areas involved are the buttocks or flexor and external surfaces of the thighs, the feet or the whole of the lower abdominal region. The discoloration is marked, presenting a dusky violet hue limited by a hyperemic zone. The contrast between the areas of discoloration and the icteroid skin surrounding them, observed in the majority of cases, is striking. The subintegumentary tissues, in pronounced cases, is involved; the hemorrhage permeates the fat, following the course of the connective tissue trabeculæ. The tissues may be generally thickened by the blood which is effused within the fat and which, in severe cases, invades even the muscles.

As to congenital hemorrhage, it may appear in the skin, usually in the form of petechiæ. Hemorrhage from the cord and mucous surfaces may also make their appearance soon after birth. Probably the most frequent early hemorrhage is in the form of hematemesis, which may begin with the effort to dislodge mucus from the pharynx or with the vomiting of meconium in instances of premature attempts at respiration. Later hemorrhages may appear from the fifth to the twelfth day. In fatal cases the termination is reached in from three to five days after the beginning of the bleeding. In cases which end in recovery, the oozing may last for two or more weeks with a gradual lessening of the amount of hemorrhage; or, more frequently, as in hemorrhage from the cord for instance, may be arrested suddenly. In intracranial hemorrhage the symptoms of pressure begin early. Cases attended with intense icterus, with fever and rapid emaciation run a rapidly fatal course. Those with sudden onset and extensive extravasation or loss of bood by internal bleeding are unfavorable. Hemoperitoneum and subarachnoid hemorrhage are the accompaniment of severe diathesis. They point usually to early death. Bleeding from the cord is not necessarily fatal. In instances of continuous oozing, even to the point of exsanguination, a sudden cessation of the hemorrhage may occur and the child begin to improve.

Internal hemorrhages vary in their form according to their

situation. In the lungs the bleeding is in the form of small apoplectic areas distributed generally (usually in the upper lobes) or peripherally in the form of infarcts. The subserous hemorrhages are usually limited to minute ecchymoses, although, as an exception to this, subcapsular hemorrhages of the liver may be extensive; it is not uncommon to find postmortem a subserous extravasation overlying both the right and left lobes of the liver divided by the suspensory ligament in the mid line and limited on either side by the costal borders. Hemorrhages in the spleen and suprarenal and thymus glands are usually in limited areas. In intraperitoneal hemorrhage the blood is usually unclotted. In subarachnoid hemorrhage the blood is held in a loosely formed clot which breaks down into fluid blood with the lightest handling. Hemorrhage affecting the mucous membrane may be in the form of free bleeding, which usually does not undergo clotting, or it may be in the form of submucous ecchymoses. The latter are seen particularly in the stomach between the rugæ, also in the upper intestinal tract. Bleeding into the connective tissue may be more or less extensive. A more or less frequent site for this form of bleeding is in the sheath of the umbilical vein.

The tendency to bleeding hinges primarily upon the comparative heightening of arterial pressure in the newborn. This is an inheritance from intrauterine life and is probably due to the limitation of the circulation by the absence of the pulmonary circuit. The comparative thickening of the adventitia in the vessel walls is corroborative of the existence of high arterial pressure. It is possible that this condition of the blood vessels may serve as a protection against the danger of a sudden reduction in the course of the circulation which results from the ligation of the cord and which may be only partially relieved by the establishment of the pulmonary circulation. It is necessary, however, to look for a more direct cause of hemorrhage than excessive pressure, otherwise the more or less common interference with the circulation, as from pressure from prolapse or winding of the cord during labor, and after labor from ligation of the cord, would be followed by hemorrhage. The pathological condition of the vessels in syphilis is confined, according to Schutz to a thickening of the walls due to an hypertrophy of the muscular layer.

In spite of these facts the arterial changes in syphilis are not sufficiently distinctive to account for the tendency toward hem-

orrhage, as far as the arterial system is concerned. At best the consideration of the arterial changes is somewhat wide of the mark, as the extravasation occurs (except in instances of hemorrhage from the cord and in some instances of intracranial bleeding) in the form of capillary oozing. It, therefore, seems more likely that the relationship between the character of the blood and the containing capillaries is disturbed. The coagulability of the blood is certainly reduced. The persistence of bleeding from the cord in spite of ligation is evidence of this. The benefit from the internal administration of drugs which are supposed to increase the coagulability of the blood, a calcium chloride, has been demonstrated in instances where ligation was entirely without effect.

Recent bacteriological research has established the infectious cause of purpura in distinct instances. It is doubtful, though, that the presence of microorganisms postmortem should point conclusively to their existence as a direct or primal cause of hemorrhage in a large number of cases. In a very interesting series of cases of infectious origin described by Hamill and Nicholson (ARCHIVES OF PEDIATRICS, September 1903), cultures made from the spleen, the lungs, the umbilical vessels and the heart's blood revealed the presence of microorganisms which in all likelihood were present in the environment of the children—in the air, possibly from the milk, upon the hands of the nurse or in the water with which the children were bathed. Conspicuous among these organisms was the colon bacillus. Relative to syphilis, however, these findings would make one incline to the view expressed by Capps (*American Journal of Obstetrics,* Vol. XLV.) that it is possible during the last few days of life for various microorganisms, especially the colon bacillus, to pass from the intestinal tract into the blood. The organism is thus to be found both in the blood and viscera after death. What applies to the colon bacillus is likely also the case with the staphylococcus aureus and the bacillus aerogenes lactis, the former being found in typical growth in four out of six cases reported by Hamill and Nicholson. Under these circumstances it is at least worthy of emphasis that the presence of microorganisms does not exclude the possibility of syphilitic infection. Further than this, syphilis is likely to play a more prominent rôle in instances of purpura ending in recovery than is infection due to the presence of microorganisms, as the latter is usually fatal.

Speaking generally, it would likewise be an error to overlook in many cases of supposedly infectious origin, syphilis, for, among other causes, notwithstanding the fact that sporadic instances of purpura due to infection may occur, it is beyond the probabilities that an infection so grave as this proves itself to be in certain instances, and in which the organisms present are found to originate in the infant's surroundings, should attack the children singly; yet in 45 cases of those noted in the records of the Lying-in Charity mentioned above none of them came in groups, the only parallel cases as to the time of occurrence being those in an instance of twins.

In the matter of diagnosis hemorrhage appears usually in children who do not present the characteristic signs of syphilis. Where this rule does not hold good the congenital manifestations, such as pallor, rhagades, shrunken skin, are more often observed than the hereditary manifestations, such as the characteristic eruption and snuffles. The more distinct types of the latter form of syphilis seem to make their appearance in cases in which the infection is more or less recent, while in the hemorrhage cases the bleeding seems to be the result of certain constitutional changes due to remote infection. The clinical manifestations which accompany hemorrhage are various, depending upon the development of the infant as to prematurity, upon the degree of blood dyscrasia, and probably upon the thoroughness of the specific infection. In my cases the following course of events and their relationship to the histories was noted:

CASE I. Death following umbilical hemorrhage, with wasting and signs of cerebral pressure. Autopsy revealed intracranial hemorrhage. The mother gave a history of infection by a former husband.

CASE II. Death in a premature infant following umbilical hemorrhage. Clinical evidences of syphilis during life in the form of vesicular eruption of the plantar surfaces. Autopsy: Subarachnoid hemorrhage, infarction of both kidneys. A history in the mother of previous miscarriage in the third month.

CASE III. Death from asphyxiation. Skin hemorrhages in the form of more or less extensive extravasation. Syphilitic enlargement of the liver, the abdominal circumference reaching 31 cm. History of syphilis in the mother. The autopsy revealed nothing of interest beyond the liver condition.

CASE IV. Death immediately following birth in a premature infant. Bleeding from the cord. Petechial eruption. Marked syphilitic degeneration of the placenta.

CASE V. Ecchymosis of the serous membrane and minute apoplectic areas in lungs revealed by autopsy. Tubercular syphiloderm in palmar surfaces. Laryngeal obstruction and marked scaling of the skin during life.

CASE VI. Hemorrhage from the mouth and cord complicated by icterus. Typical manifestation of congenital syphilis in the form of emaciation and pallor. Autopsy: Chronic hepatitis and suprarenal hemorrhage.

CASE VII. Hemorrhage from the cord. Death following inanition in the course of suppurating gummata of the scrotum and great toe. No autopsy.

CASE VIII. Stillborn infant. Gumma on the external border of both feet. Scleral hemorrhage. Autopsy: Subarachnoid hemorrhage, enlargement of the thymus.

CASE IX. Stillborn infant. Subcutaneous extravasation. Evidence of leakage from the cord after ligation. Bullous eruption of the palmar and plantar surfaces.

CASE X. Stillborn infant. Cutaneous hemorrhage. Autopsy: Pericranial and subperiosteal hemorrhage, subcapsular hemorrhage of the liver. Syphilitic periosteitis and necrosis of the cartilage of the nose, in the mother.

Perhaps the most interesting clinical accompaniment of hemorrhage is icterus. It is present in some degree in almost every case. According to one theory icterus is a primary condition, which is followed by hemorrhage due to its toxic effect. Excessive jaundice usually increases the gravity of the outlook. There is no doubt that the presence of bile in the blood decreases its coagulability, showing that the bile has probably a disintegrating effect upon the blood. It seems more likely, however, considering the large number of children affected with jaundice without consequent hemorrhage, that it is secondary to the blood changes that produce hemorrhage. It may be, on the other hand, that, in weakly children, the invasion of the blood by bacteria present in the intestinal tract may give rise to jaundice, the result of their toxic action, so that in some cases the icterus may be a mere accompaniment of the hemorrhage condition.

As to the conditions found postmortem, Behrand found in a

case with a clear history of syphilis pulmonary lesions consisting of subpleural effusions with white hepatization and numerous gummatous nodes. The infant was born with a petechial eruption. In two of the cases described in the foregoing portion of this paper, apoplectic points were found in the lungs. The combination of hemorrhages with other pulmonary evidence of syphilis in the lungs is, in the writer's opinion, rare. The only instance among the cases of congenital syphilis in the writer's experience in which gummata were found in the lungs was one without accompanying hemorrhage. Behrend mentions, also, in the case alluded to, a fatty degeneration of the pappillæ of the heart muscle.

Fischl, on the other hand, in a case of hemorrhagic syphilis found that the musculature of the heart was not markedly altered. Fatty degeneration was not apparent; the nuclei were sharply outlined and lightly stainable. Beneath the pericardium small hemorrhages were to be seen, penetrating at individual points into the muscular surface.

Syphilitic children with evidence of internal hemorrhage require prompt treatment. The effort should be to sustain their flagging powers of resistance. Oil baths, alternating with mercurial inunctions, are indicated. The child, however, should be kept in the incubator and disturbed as little as possible, except for the necessary measures of treatment. In fact, rest is the first indication. For fever the ice cap is indicated. In intracranial hemorrhage the latter is directly useful as a local measure. In extensive skin hemorrhages rubbing for the purpose of carrying out inunctions should be omitted. In severe cases of melena peristalis should not be encouraged. With this in view the nourishment should be given frequently in small quantities and dry warmth should be applied to the body.

The following drugs have been used internally: Suprarenal extract, half grain doses repeated. Adrenalin, solution, 1-1000, one drop, in repeated doses. Gelatin water, in the proportion of two drams to one pint. Fluid extract of ergot, one drop doses. Talley, in an interesting case in which continuous bleeding resulted from a puncture (alluded to above), noted a favorable result from the use of calcium chloride in half grain doses given every two hours.

DEPARTMENT OF ABSTRACTS

Conducted by
MICHAEL A. BRESCIA, M.D., NEW YORK

WALLERSTEIN, R. O. AND HOAG, M. S.: TREATMENT WITH IRON-DEXTRAN OF IRON-DEFICIENCY ANEMIA IN CHILDREN. (Journal American Medical Association, 164:962, June 29, 1957).

Hematological values were studied in 24 infants with iron-deficiency anemia before and after treatment with intramuscular doses of iron-dextran. Hemoglobin values rose to about 11 Gm./100 ml. in three weeks. Rises of 4 per cent per day were seen in several infants with severe anemia. Reticulocyte response occurred early and correlated fairly well with the degree of anemia in patients with severe cases; it was inconstant in patients with moderate anemia. There were no untoward effects from the iron injections. Imferon (an iron-dextran complex containing the equivalent of 50 mg. of iron/cu.ml.) given intramuscularly appears to be a safe, effective, and convenient form of iron treatment in infancy. AUTHORS' SUMMARY.

MOORE, H. A. AND LARSEN, G. I.: PRESENT DISTRIBUTION OF DIPHTHERIA IN THE UNITED STATES. (Public Health Reports, 72:537, June 1957).

While diphtheria case rates and death rates have decreased in recent years, the case fatality rate has changed little. A need to inquire into the promptness of diagnosis and the completeness of reporting is suggested. The persistent diphtheria problem in the United States is tending to localize in the South Atlantic, East South Central and West South Central States. Outbreaks of diphtheria have been observed in these areas but not exclusively so. Localized sharp outbreaks have occurred in recent years in Idaho, Nebraska, Minnesota, South Dakota, and other northern and western States. During 1955, outbreaks of diphtheria were observed in diverse regions and in all months of the year. The populations affected were variously white, nonwhite, and Latin-American. Both rural and urban areas were involved.

AUTHORS' SUMMARY.

BOOK REVIEWS

Conducted by
MICHAEL A. BRESCIA, M.D., NEW YORK

CHILD HEALTH AND DEVELOPMENT. 2ND ED. Edited by Richard W. B. Ellis, O.B.E., M.A., M.D., F.R.C.P. Cloth. Pp. 525. Illustrated. Price $6.75. London: J. & A. Churchill Ltd., 1956.

This book, by various authors, is divided almost equally into two parts. The first is devoted to development from birth to adolescence, and the second part to the social aspects of child health. The section on development is well done and adequately illustrated and proper emphasis is placed on the emotional as well as the physical development. In this regard the book differs from most texts on pediatrics in giving equal if not greater consideration to the emotional aspects of development. The second part of the book considers the technical aspects of child health as it is influenced by the pre-nursery schools, nursery schools, schools of the normal and handicapped, etc. as these problems are handled in England. This is not of great concern to the American pediatrician, with the exception of those who are particularly involved with these public services. M.A.B.

CASE OF FAVISM. N. A. BOLT. (Nederl. tijdschr. geneesk., 99:1651-1655, June 4, 1955). Bolt presents the history of a 3-year-old boy, whose mother noted one day that he became very quiet, though ordinarily he was lively, that his skin was yellow, and that he became drowsy and fell asleep. He was fed on awakening but he vomited, and his urine was brownish-black. Abdominal pain developed and recurred after another period of sleep. Examination suggested a sudden severe hemolysis. Poisoning, possibly with the insecticide parathion, was thought of, but the clinical picture differed from parathion intoxication. After a transfusion of 300 cc. of blood and other measures, the boy recovered. The true cause of the hemoglobinemia and hemoglobinuria was not ascertained until the author read A. H. Becker's report (*J.A.M.A.* 155:1158 [July 24] 1954) on the treatment of favism with cortisone. It was then recalled that fava beans (Vicia faba) were among the foods consumed by the child before the onset of his illness. —*J.A.M.A.*

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Doctors prescribe "TLC" (tender, loving care) to insure healthy growth for babies everywhere. For most children this is provided by their own mothers and fathers but, for many, someone else must bear the responsibility. You give "TLC" to such as these when you give the United Way through your United Fund or Community Chest . . . and when you give, you also help troubled men and women, people who are ill or handicapped, boys and girls who need healthy, constructive leisure time activities and old people who also need tender, loving care.

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BUILD SOUND BODIES DURING CRITICAL FORMATIVE YEARS

Pluravit Drops

A pleasant lime flavored, readily dispersible combination of 8 essential vitamins

Each 0.6 cc. contains:

Vitamin A	5000 units
Vitamin D_3	1000 units
Vitamin B_1	1 mg.
Vitamin B_2	0.4 mg.
Vitamin B_6	1 mg.
Nicotinamide	5 mg.
Pantothenic acid	2 mg.
Vitamin C	50 mg.

Stable • Mixes Readily

DOSAGE: Infants 0.3 cc., children and adults 0.6 cc. daily. May be taken directly or mixed in milk, fruit juices, or other food.

How supplied: Bottles of 15 and 50-cc. with graduated dropper.

Winthrop LABORATORIES
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